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Effect of Processed Foods on Advanced Glycation End Products: Cancer Cases

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Abstract: Advanced glycation end products (AGEs) are heterogeneous compounds that occur endogenously and exogenously during metabolism. These compounds increase because of processed food consumption. Nowadays, fast-paced living conditions lead individuals to consume processed food. High numbers of processed foods consumed because of nutrition cause inflammation in metabolism. Inflammation causes atherosclerosis, diabetes, kidney diseases, cancer, liver, and some neurodegenerative diseases. The purpose of this review study was to detail the relationship between AGEs and some types of cancer depending on nutrition and dietary habits. For this purpose, cancer types such as breast cancer, colorectal cancer, and pancreatic cancer, which have been common in recent years, were discussed. AGEs bind to receptors on cells, affect certain transcription factors, prevent cancer cell apoptosis, and support proliferation. Studies have shown that the number of AGEs is affected by nutrition and dietary habits. In this context, it has been shown that phenolic compounds, vitamins, and limited AGE intake play an important role in minimizing the effects of these products. This review study revealed the effects of AGEs on cancer and examined in detail the conditions that affect the formation of these products. When the studies are evaluated, it is aimed to raise public awareness by emphasizing that the formation of advanced glycation end products is directly related to nutritional habits and food processing methods, that it causes different diseases, especially cancer, and how its formation can be limited.

Keywords: Glycation, advanced glycation end products, nutrition, cancer.

İşlenmiş Gıdaların İleri Glikasyon Son Ürünlerine Etkisi: Kanser Vakaları

Özet: İleri glikasyon son ürünleri (İGS) metabolizmada endojen ve eksojen olarak oluşan heterojenik bileşiklerdir. Bu bileşikler işlenmiş gıda tüketimine bağlı olarak artmaktadır. Günümüzde hızlı ve tempolu yaşam koşulları bireyleri işlenmiş gıda kullanımına yönlendirmektedir. Beslenme sonucunda alınan yüksek miktarda işlenmiş gıdalar metabolizmada inflamasyona neden olmaktadır. İnflamasyon ise metabolizmada ateroskleroz, diyabet, böbrek hastalıkları, kanser, karaciğer ve bazı nörodejeneratif hastalıkların oluşumuna neden olmaktadır. Bu derleme çalışmasının amacı ise İGS’ler ile bazı kanser türleri arasındaki ilişkiyi beslenme ve diyet alışkanlıklarına bağlı olarak detaylandırmaktır. Bu amaçla son yıllarda sık rastlanan meme kanseri, kolorektal kanser ve pankreas kanseri gibi kanser türleri ele alınmıştır. İGS’lerin hücrelerdeki reseptörlere bağlanarak belirli transkripsiyon faktörlerini etkileyip kanser hücrelerinin apoptozunu engellediği ve proliferasyonu desteklemektedir. Yapılan çalışmalar, beslenme ve diyet alışkanlıklarına göre İGS’lerin miktarlarını etkilediğini göstermektedir. Bu bağlamda fenolik bileşiklerin, vitaminlerin ve kısıtlı İGS alımının, bu ürünlerin etkilerini en aza indirmede önemli rol oynadığı gösterilmiştir. Bu derleme çalışması, İGS’lerin kanser üzerindeki etkilerini ortaya koyarak, bu ürünlerin oluşumunu etkileyen durumları detaylı bir şekilde incelemiştir. Çalışmalar değerlendirildiğinde, ileri glikasyon son ürünlerinin oluşumunun beslenme alışkanlıkları ve gıda işleme yöntemleriyle direkt olarak ilişkili olduğunu, kanser başta olmak üzere farklı hastalıklara neden olduğunu ve oluşumunun nasıl sınırlandırılabileceği vurgulanarak, kamu bilincinin oluşturulması hedeflenmiştir.

Anahtar Kelimeler: Glikasyon, ileri glikasyon son ürünleri, beslenme, kanser.

Review

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1.Introduction

Glycation (Glycosylation) is a biochemical process involving the interaction of carbohydrates with free amino groups in lipids and nucleic acids through "*maillard*" or "*browning reactions*". These reactions can result from high-temperature cooking or prolonged slow-cooking processes (Dariya and Nagaraju, 2020).

Glycation reactions lead to the formation of advanced glycation end products (AGEs). They can be classified based on their formation as endogenous (formed in the organism) or exogenous (formed through lifestyle factors such as nutritional habits, smoking, etc), their molecular weight as heavy or light, or their toxicity properties as toxic or non-toxic. One of the exogenous sources, dietary AGEs, can be associated with an individual's eating habits. Examples of glycation products acquired through diet include Nε-carboxymethyl-lysine (CML), Nε-1-carboxyethyl-lysine (CEL), methylglyoxal (MGO), pyrraline, and glycolaldehyde. Dietary AGEs (dAGEs) formed by the interaction of exogenous proteins and carbohydrates at high temperatures occur more rapidly than endogenously formed AGEs. Therefore, dietary habits are known to increase the rate of AGEs (Gill et al., 2019; Lugt et al., 2020; Rungratanawanich et al., 2021; Twarda-Clapa et al., 2022).

Accumulation of AGEs in the body leads to various health problems and metabolic effects such as insulin resistance, lipid resistance, arterial stiffness, inflammation, tissue damage, apoptosis, bone cell injuries, cellular stress, neurodegeneration, hepatic fibrosis, and cirrhosis. Moreover, these products trigger hyperlipidemia, oxidative/carbonyl stress, antioxidant deficiency in the body, and aging. Because of these reactions, the onset and progression of numerous diseases, including cancer, diabetes, kidney diseases, heart diseases, osteoporosis, aging, gout, and liver diseases, are observed. In addition, some factors such as diabetes, age, gender, smoking, obesity, and lifestyle are known to influence the increase in glycation (Ahmad and Farhan, 2016; Dariya and Nagaraju, 2020). Recent and ongoing studies continue to explore the impact of AGEs on various health conditions. The objective of this study was to investigate the formation of AGEs and their association with cancer types such as breast, pancreas, and colorectal cancers, shedding light on the factors influencing AGE formation (Uribarri et al., 2010; Rungratanawanich et al., 2021) (Figure 1).

2. What are AGEs and Theirs Effects on Metabolism?

AGEs, which are a natural mechanism in the body, are known to have a high potential for toxicity because of the quantity of production and types of binding. These products are formed through the glycation, oxidation, and carbonylation pathways. The Maillard reaction, representing the initial step of glycation, involves the nucleophilic reaction between a free amino group of a protein (such as lysine, arginine, or cysteine) and a carbonyl group of a sugar molecule (glucose, fructose, etc.). These two compounds undergo a chemical reaction to form a Schiff base, which is then re-arranged intra-molecularly into a more stable ketoamine or Amadori product (AP) within hours. These glucose-modified proteins undergo advanced reactions to form AGEs. They occur through irreversible reactions, leading to protease-resistant cross-linking of peptides and proteins, contributing to protein accumulation and amyloidosis (Ahmed, 2005; Vicil and Ulutaş, 2020).

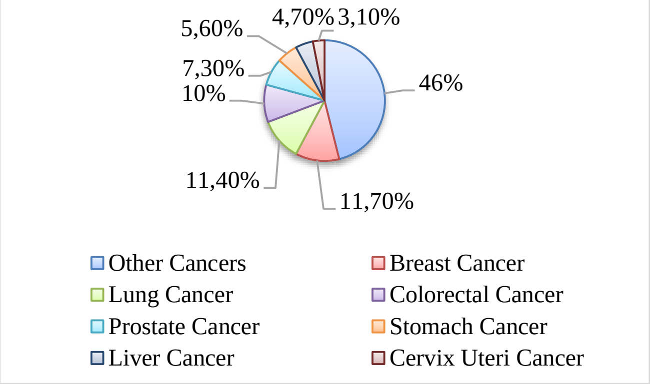

Figure 1. Estimated number of new cases in 2020 (WHO, 2023).
Şekil 1. 2020'de tahmini yeni vakalar (WHO, 2023).

Moreover, the cross-linking of long-lived proteins by AGEs is known to accelerate the normal aging process of cells and tissues. AGEs can be found in various forms of lipoproteins and lipid components, contributing to problems such as macroangiopathy, microangiopathy, and amyloidosis. Studies have suggested some diseases such as atherosclerosis, cataracts, diabetes, inflammation, cancer, kidney and liver diseases, and neurodegenerative problems by AGE formation. Although the pathological properties of AGEs were initially attributed primarily to chemical features such as protein cross-linking, recent studies indicate that AGEs also impact cellular processes and signaling. AGEs can directly bind to extracellular membranes or interact with cell surfaces through specific receptors (RAGEs) (Lyu et al., 2023).

When we evaluated recent studies, it was observed that AGEs can alter the structure, tissue, activity, and other characteristics of cell matrix proteins by cross-linking them. Glycation reactions have changed collagen and elastin, proteins in the extracellular matrix membranes. Through this process, collagen can change endothelial cell activity, leading to the formation of atherosclerotic plaques. In terms of biochemical insight, a recent study suggested that CML may increase vascular calcification through activation of pyruvate dehydrogenase kinase 4. These correlated atherosclerotic plaques and vascular calcification are interrelated problems that can lead to renal failure, coronary artery disease, and oxidative stress (Zhu et al., 2018).

When examining the mechanisms through which AGEs may cause diseases, it can be said that they play a significant role in diabetes complications. In these complications, AGEs bind to specific cell receptors, triggering various signaling pathways. The receptors most commonly bound by AGEs in the body are referred to as the receptor for advanced glycation end products (RAGE). RAGE, belonging to the immunoglobulin superfamily, is a transmembrane receptor and is the most commonly bound receptor by AGEs in humans (Jangde et al., 2020).

Many diseases occur because of AGE binding to RAGEs. The production of RAGE increases in various metabolic conditions such as diabetes and inflammation. RAGEs are found in many cells throughout the body, including macrophages, endothelial cells, neurons, and connective tissue cells. When bound to RAGE, AGEs activate extracellular and intracellular pathways. As a result of these reactions, a transcription factor called NF-κB (nuclear factor-kappa B) can become active (Asadipooya and Uy, 2019).

This activated transcription factor increases the expression of inflammatory cytokines, adhesion molecules, and other cellular mediators. These changes lead to increased oxidative stress, production of proinflammatory cytokines, increased expression of adhesion molecules, changes in procoagulant factors, and vasoconstriction (Asadipooya and Uy, 2019).

3. Nutrition and Cancer Risk: Biochemistry of AGEs/RAGEs

Accumulation of AGEs and their metabolites such as α-dicarbonyls such as methylgloxal, glyoxal, and diacetyl results in dysfunction of proteins, nucleotide bases, and DNA repair enzymes. Although tumor cells use the same metabolic network as normal cells, they have re-programmed metabolism to meet uncontrolled replicative demands. AGEs/RAGE increase the glycolysis pathway and trigger inflammatory cytokines with NF-κB. Depending on increased glycolysis and inflammatory cytokines, the amount of inflammation around the tumor also increases (Rojas et al., 2010). AGEs play a pivotal role 25% of all cancer types and increase tumorigenic signaling pathways; they are responsible for low oxygen levels (hypoxia) around tumor cells and inflammation (Xu et al., 2010). The AGEs–RAGE interaction activates NADPH oxidases and produces reactive oxygen species (ROS) under hypoxic conditions. These trigger interactions between hypoxia and AGEs. Hypoxia also causes the formation of new blood vessels around active cancer cells. Increased cancer cells facilitate the nutrition and proliferation of cancer cells. *In vitro* and *in vivo* studies have shown that blocking RAGE can suppress invasive capacity and angiogenesis (Liang et al., 2011; Nedić et al., 2013).

In metabolism there is mechanism that called "autophagy" to reduce wear and tear of tumor cells. It minimizes stress by breaking down damaged cellular components and ensuring cell survival and resistance to death. The key inhibitor of this process is the target of rapamycin (mTOR) and its regulator, AMP-activated protein kinase (AMPK). The AGEs–RAGE interaction maintains autophagy by reducing mTOR phosphorylation and ensures the survival of tumor cells. In addition, RAGE increases proliferation resistance by activating the AMPK/mTOR signaling pathway and regulating autophagy (Li et al., 2018). The effects of AGEs and RAGEs on the recent increase in cancer are diverse. For example, their role in various cancer types, such as pancreatic, colon, and breast cancer, has been emphasized.

Considering that cancer is currently an increasing public health problem, it is important to highlight the role of factors such as food safety, processed foods, and dietary habits in cancer formation. AGEs in foods play a crucial role in this age. In this review, we will explore in-depth the relationship between AGEs and cancer, providing examples of how this mechanism is effective in different cancer types (Figure 2).

3.1 Breast cancer

Breast cancer typically originates in breast tissue and often manifests in the mammary glands (milk-producing glands) or milk ducts (channels carrying milk to the mammilla). Cancer usually begins with uncontrolled and abnormal cell growth in the breast tissue. According to World Health Organization (WHO) data, in 2020, 2.3 million women worldwide were diagnosed with breast cancer, resulting in 685.000 deaths attributed to this disease. By the end of 2020, 7.8 million women who had been diagnosed with breast cancer in the last 5 years were alive, establishing it as the most prevalent cancer globally. This cancer type is more frequently observed in women over 40 years old compared with other age groups (Abdulrahman and Rahman, 2012). 5-10% of women, the

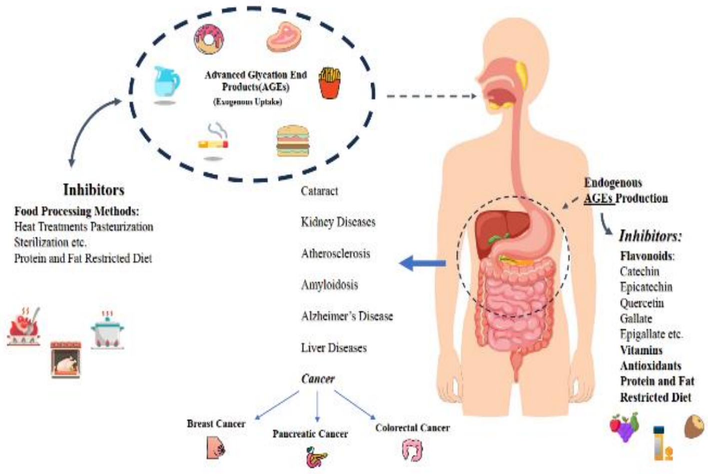

Figure 2. AGE sources and their relationship with diseases.
Şekil 2. İleri Glikasyon Son Ürünlerinin kaynakları ve ilişkili hastalıklar.

development of this cancer type is known to occur due to the inheritance of an autosomal dominant gene, often involving mutations in the breast cancer gene 1 and 2 (BRCA1 and BRCA2) genes. In addition, risk factors for breast cancer include female reproductive hormones (endogenous and exogenous), nutritional factors (especially dietary AGEs intake), benign breast disease, re-productive history, and environmental factors. Treatment involves radiotherapy, chemotherapy, andsurgical interventions. Breast cancer represents the most prevalent form of cancer and is the primary contributor to cancer-associated mortality among women globally (Maxwell and Nathanson, 2013; Alexander et al., 2010). Moreover, there is a significant association between diabetes and breast cancer. Several studies and experiments have demonstrated a connection between diabetes and breast cancer. The most prevalent in circulation in individuals with diabetes is glycated albumin. In a study conducted by Sharaf et al. using a breast cancer cell line, the effects of methylglyoxal-derived bovine serum albumin AGEs on cell proliferation, migration, and invasion were examined (Sharaf et al., 2023). The results indicated that MGO-BSA-AGEs increase proliferation, migration, and invasion of breast cancer cells, and these effects occur through the AGEs receptor (RAGE). Blocking this receptor has been suggested to eliminate the observed changes (Sharaf et al., 2023). MGO-BSA-AGEs, through RAGE, enhance certain unwanted activities within the cell and regulate cancer cell invasion and migration by contributing to other signaling proteins (Sharaf et al., 2023). In another study conducted in 2023, focus was on carboxymethyl lysine (CML), an important dAGE. The research divided participants into two groups: PG (breast cancer group) and CG (control group). Subgroups within PG, HER2+ (HER2−), were examined. HER2+ groups consist of breast cancer cells with HER proteins on their surfaces, while HER2− groups lack these proteins. Generally, HER2-negative breast cancer can be a slower-growing form. Analysis of serum markers in the study revealed no significant difference in serum CML and RAGE levels between PG (breast cancer group) and CG (control group). Additionally, a comparison between HER2+ (groups showed that, at the T1 (tumor not spreading to surrounding tissues) stage, despite no significant differences in energy intake, the dCML level of the HER2− group was significantly higher than that of the HER2+ group. These findings suggest that the dietary habits and serum CML levels of HER2- breast cancer patients may contribute significantly to DNA damage, inflammation, and protein oxidation effects at the T1 stage compared with HER2+ patients (Alkan et al., 2023).

3.2 Colorectal cancer

According to the WHO, colorectal cancer is the third most prevalent cancer worldwide, constituting approximately 10% of all cancer cases and ranking as the second leading cause of cancer-related deaths globally. It predominantly affects individuals over the age of 50. Colorectal cancer is characterized by the development of a tumor or abnormal tissue growth in the inner lining of the rectum or colon, which can give rise to a tumor on the rectum or colon wall if it transforms into cancer. Subsequently, it may increase the chances of metastasis to other areas by growing into blood or lymph vessels. Tumor types resulting from the growth of mucous-producing glands covering the colon and rectum are the most frequently observed pathogenic factors in this cancer, termed adenocarcinoma. Among other cancers in the colorectal region are tumors originating in hormone-producing intestinal cells, tumors arising in Cajal cells, which are colon cells, lymphomas related to the immune system in the colon or rectum, and sarcomas that typically begin in blood vessels but can rarely occur in colorectal walls. It is a prevalent disease among individuals aged 65-74, with a higher prevalence in women. Factors such as obesity, diabetes, genetic factors, sedentary lifestyle, poor dietary habits (high in fat and protein), smoking, and aging actively contribute to the development of colorectal cancer (Xi and Xu, 2021; Alzahrani et al., 2021)

Furthermore, AGEs and receptors for AGEs (RAGEs) have various effects on the initiation and progression of colorectal cancer (CRC). Several genes interacting with RAGEs are implicated in CRC formation. For example, recent studies have revealed that a protein released during inflammatory conditions limits apoptosomal caspase-9 activation. On the basis of these findings, this protein may play an apoptotic inhibitory role in colon cancer, reducing anticancer immune responses through stimulated apoptosis in immune cells. Among other examples are genes of the S100 family, including S100A8/A9, S100A4, and S100P, which are associated with colorectal cancer. Studies suggest that these proteins could serve as potential biomarkers associated with colorectal cancer (Azizian-Farsani et al., 2020).

Following the diagnosis of colorectal cancer, the consumption of high-sugar food products is associated with higher mortality. The metabolic pathways of glycolysis and fructolysis are suggested to contribute to the formation of a group of compounds known as "glycer-aldehyde-derived advanced glycation end products" (glycer-AGEs). Different types of glycer-AGEs, such as 3-hydroxy-5-hydroxy-methyl-pyridinium compounds (GLAP) and triosidine, have been identified. Glycer-AGEs are found in high-glucose and high-fructose foods (bread, corn sirup rice, etc.). Glycer-AGEs also possess pro-inflammatory and pro-oxidant properties, contributing to colorectal cancer progression and increased mortality. In addition, the binding of glycer-AGEs to RAGEs results in the release of pro-inflammatory cytokines, increased cellular damage, and elevated vascular endothelial growth factor (VEGF) expression in cancer cells. In a cohort study named EPIC conducted at Kanazawa University in Japan, serum concentrations of glycer-AGEs from 1034 colorectal cancer patients were measured using a competitive enzyme-linked immunosorbent assay (ELISA). Higher serum glycer-AGE concentrations were statistically significantly associated with higher CRC-specific and all-cause mortality (Mao et al., 2023).

3.3 Pancreatic cancer

The pancreas is a vital organ that plays a key role in digestion and metabolic processes. It produces the necessary enzymes and hormones for digestion and regulates blood sugar by facilitating the production of insulin and glucagon. Pancreatic cancer is a type of cancer that results from the uncontrolled and abnormal growth of cells in the pancreas, an organ responsible for these functions. A significant proportion of pancreatic cancer cases involve rapidly spreading ductal adenocarcinomas, typically occurring in the head of the pancreas. Because of its aggressive nature, pancreatic cancer exhibits rapid metastasis, contributing to a high mortality rate. According to studies, cancer is expected to be the second leading cause of cancer-related deaths by 2030 (Koçatakan and Ataseven, 2021).

Factors influencing the development of pancreatic cancer are similar to those of other cancers, including obesity, diabetes, alcohol consumption, smoking, substance abuse, age, and genetics. Recent studies indicate that AGEs are found in higher quantities in obese and diabetic individuals than in normal ranges, and this is identified as a factor facilitating the progression of pancreatic cancer. Menini et al. (2021) conducted studies on mice to explore the relationship between CML and pancreatic cancer. It was observed that CML acts as a substance that promotes the proliferation of cells, such as MIA PaCa-2 and PANC-1, and this effect occurs depending on the concentration and duration of exposure to CML. The more CML present and the longer the exposure, the greater the cell proliferation. In addition, even low concentrations of CML induce responses in human pancreatic duct epithelial (HPDE) cells. While these proliferations are part of the cell's life cycle, disturbances or abnormalities in these control mechanisms can lead to uncontrolled cell proliferation, increased formation of RAGEs, and potentially tumor formation (Menini et al., 2021). Another result indicates that CML treatment increases the activity of genes such as p-STAT3, NFATC1, and PIM1, and it may increase the levels and activation of NK-κB/p65 protein, potentially contributing to the development and acceleration of pancreatic cancer (Menini et al., 2021).

In another study, it was found that the protein RAGE stimulates the formation of neutrophil extracellular traps (NETs) through neutrophils in pancreatic cancer. NETs are immune products that respond to pathogens, but an excess of NETs can lead to serious damage in tissues and progression of advanced diseases such as cancer. In mice with RAGE deficiency, reductions in NET formation in pancreatic cancerous mice and decreased levels of circulating DNA are known. These findings indicate that RAGE promotes NET formation through neutrophils. Moreover, high levels of autophagy were detected in neutrophils obtained from pancreatic cancerous mice, and inhibition of autophagy (chloroquine treatment) resulted in decreased NET formation. Similarly, treatment in patients reduces serum DNA levels (Boone et al., 2015).

Hypoxia, which occurs in cancer conditions, causes RAGE to bind with oncogenic Kras (gene of cancer), which promotes tumor growth. Oncogenic Kras refers to a mutated (altered) form of the Kras gene, which has a regulatory effect on normal cell growth and division. However, RAGE deficiency inhibits Kras signaling in vitro and increases pancreatic tumor cell death under hypoxic conditions (Shahab et al., 2018).

These studies suggest significant interactions between RAGE and pancreatic cancer. Recently, particular interest and attention is the resistance of RAGE to gemcitabine, a cytotoxic drug used in the treatment of pancreatic cancer. In a study by Swami et al. (2021), RAGE inhibition was achieved in experimental mice with pancreatic cancer. This inhibition was shown to reduce autophagy induced by gemcitabine in pancreatic tumors. Autophagy is a process by which organelles and proteins within the cell are broken down. In this study, it was shown that this process increased in tumors treated with gemcitabine. TAGEs inhibition by reducing autophagy in mice treated with gemcitabine, could regulate autophagic processes within cells. This understanding emphasizes the role of RAGE in regulating apoptosis in tumor cells, highlighting its potential contribution to the development of new treatment strategies for such tumors (Swami et al., 2021)

4. Alternative Measures for Inhibiting AGEs

4.1. Nutrition

In the previous sections of this study, advanced glycation products formed because of excessive glycation in the body and the receptors of these products found in most cells in the body (RAGE) were mentioned. The excess of these products in the body and the health problems caused by this excess (especially cancer) have been addressed. AGEs must be present in some amount in the body for the natural flow of the body, but there are precautions to be taken in excess.

In this part of our review, we will discuss the measures that can be taken to prevent advanced glycation and excess of the products formed, and how these measures can be taken. Flavonoids are a group that ensure that the number of AGEs is kept under control. Flavonoids are a broad group that are usually found in fruits, plants, cereals, nuts, and vegetables and carry a phenolic or polyphenolic group. Foods containing flavonoids are considered to be the most common natural products in the human diet. In addition to inhibiting the AGEs of flavonoids, it is involved in the prevention of many chronic diseases, oxidative stress, and serious diseases such as cancer. Examples of the flavonoids most commonly found in nature are quercetin, kaempferol, myricetin, luteolin, apigenin, catechins, epicatechin, epicatechin gallate, and naringenin. Catechin, which belongs to the flavonoid group, is a powerful antioxidant. After being taken into the body, it affects the digestion of proteins during gastrointestinal digestion, regulates the release of free amino acids, and changes the particle size. The same catechin inhibits the release of AGEs during digestion with complexes formed by their combination with proteins (Ullah et al., 2020; Wu et al., 2021).

Epicatechin gallate (ECG) also inhibit AGE. In a study conducted, the interaction of ECG, a known AGE, with BSA (large flour albumin) was evaluated. Because of this evaluation, the ECG is wrapped by certain amino acid residues. Various bonds, such as pi-σ, pi-anion, alkyl, and hydrogen bonds, were formed between the ECG and these amino acid residues. Because of the formation of hydrogen bonds, the ECG–BSA complex was formed. Due to this complex, ECG inhibited BSA glycation and provided stabilization (Wu et al., 2019).

A study on one of the natural components, styrylflavonoids, found that they had an anti-inflammatory effect on inflammation linked to advanced aging. The majority of the inflammation caused by AGEs are eliminated by treatments using these and related flavonoid derivatives (Zhou et al., 2022). Except for these studies, many flavonoids inhibit or reduce the production of AGEs. Flavonoids are found in most foods and have a very important role in nutrition (Bestil and Uysal, 2023). In the table below, the nutrients and flavonoids contained are compiled (Table 1).

Another group of molecules that decrease protein glycation in the body and inhibit AGEs are vitamins. Vitamin D influences the mechanisms of aging, especially in many in vitro, animal, and human studies. Vitamin D reduces AGE levels and increases RAGE levels in cases of deficiency and pathological conditions. sRAGEs, unlike RAGEs, compete with this receptor and bind to circulating AGEs, a form that prevents intracellular adverse effects. Simultaneously, vitamin D treatment can be effective in reducing RAGE expression in some pathological conditions. The inhibitory effects of vitamin D on AGE receptors are realized through various cellular signaling pathways, such as MAPK/NF-κB and ADAM10/MMP9 (Kheirouri and Alizadeh, 2020). According to another study conducted in recent years, it is related to the effect of ascorbic acid on AGEs. According to the results of a study conducted in patients with diabetes, vitamin C supplementation added to patients' hypoglycemic medications caused a significant decrease in oxidative stress markers such as AGEs (Rabizadeh et al., 2023).

Dietary habits can affect the formation of glycation products. In particular, foods high in protein and fat content may contain high levels of AGEs. This phenomenon arises because protein and fat undergo more significant reactions during food processing procedures compared with carbohydrates. Based on this information, foods high in protein and fat content, such as meat, dairy products, cheese, and fatty foods, may contain higher levels of AGEs than those with lower carbohydrate content. At this point, our eating habits can prevent the formation of AGEs and reduce these harmful effects (Uribarri et al., 2010).

There have been different studies and research on the determination of dAGE intake over the years. For example, in Spain and France, it has been decided that the intake of CML, a known AGE, should range from 34 to 252 µg/kg of body weight per day, and excess is harmful to health. In the analysis of study outcomes, it became evident that the category with the highest AGE content comprised meats. Although fats actually tend to contain more dietary AGEs in quantity, they cause more dAGE intake because meats are presented to the consumer in a larger portion than fats. When the meat groups prepared by the same methods were compared with each other, the highest levels of dAGEs were observed in beef, chicken, pork, and fish.

Table 1. Flavonoids obtained from foods and their AGE activities

Tablo 1. Gıdalardan elde edilen flavonoidler ve AGE aktiviteleri.

Systematic Names	Foods	Flavonoid Contents	Activity	Cited
Glycine max	Soybeans	Genistein, Daidzein, Glycitein, isoflavone	Anti-AGEs	Milkovska-Stamenova et al. (2019), Wu et al. (2020)
Cinnamomum verum	Cinnamon	Epicatechin (EC), Catechin	Anti-AGEs	Yang et al. (2018)
Allium cepa	Onion	Quercetin	Anti-AGEs	Khan et al. (2020)
Malus domestica	Apple	Phloridzin, Quercetin, Myricetin	Anti-inflammatory	Millán-Laleona et al. (2023)
Prunus dulcis	Almond	Catechin, EC, Naringenin, Kaempferol	Anti-inflammatory	Khan et al. (2020)
Camellia sinensis	Green and black tea	Catechin, Epicatechin, Theaflavin	Anti-inflammatory	He et al. (2021), Luo et al. (2022)
Spinacia oleracea	Spinach	Patuletin and Spinacetin	Anti-AGEs	Gutierrez et al. (2020)
Prunus persica	Peach	Quercetin, Genistein, Anthocyanins	Anti-AGEs	Maatallah et al. (2020), Bento et al. (2022)
Zingiber officinale	Ginger	Quercetin, gingerol, kaempferol	Anti-inflammatory	Xue et al. (2022)
Vaccinium Vitisidae	Lingonberry	Cyanidin-3-galactoside, Cyanidin-3-glucoside	Anti-CML	Račkauskienė et al. (2019), Maduma (2022)

Lamb meat, on the other hand, was ranked lower than other meats. However, what actually attracts attention in these results is that lean meats contain very high amounts of dAGEs, despite being subjected to heat treatments under dry heat. The reason for this condition is the reactive amino-lipids found in meat and reducing sugars such as fructose or glucose-6-phosphate. At the same time, high-fat foods such as butter, cream cheese, margarine, and mayonnaise are also among the foods rich in RAGE, and their intake should be restricted (Delgado and Andrade, 2016).

The AGEs content of vegetables and fruits is considered to be quite low. For example, carrots have 10 kU/100g, tomatoes have 23 kU/100g, bananas have 9 kU/100g, and cucumbers have 31 kU/100g levels of AGEs. The reason is that these foods have high water content and low protein and fat content.

In addition, vegetables and fruits are rich in antioxidants. There are studies showing that antioxidants reduce the AGE content of foods. In particular, it has been shown in recent studies that red grape peel extract (RGSE)", effectively inhibits the formation of CML because of the antioxidants it contains. For sweeteners and desserts, the results are variable. The numbers of AGEs named GO and MGO in high-fructose corn sirup commonly used in the food industry are 50.8 and 88 µg/100 g, respectively. At the same time, as another example, fruit pulps, which are an important traditional dish in Turkey, are obtained by drying the fruit puree of different fruits such as apricots, plums, and mulberries. Unfortunately, these products have a high MGO content. It is thought that the high amount of MGO in nuts containing pesticides is due to their fat and protein content (Lo et al., 2008; Jariyapamornkoon et al., 2013; Yusufoglu et al., 2020; Nowotny et al., 2018).

When considering dairy products, the situation varies. Processing methods (pasteurization, sterilization, UHT process, etc.) during the course, changes in the levels of AGEs such as CML (Ne-(carboxymethyl) lysine) and pyrroline in different dairy products were observed. For example, as dairy products go through processing processes, the amount of AGEs decreases in some cases, whereas increases are observed in others. Higher AGE levels were found in condensed products such as powdered milk and protein-rich items based on the observed results. Changes in the number of AGEs because of nutrient processing will be examined in more detail in the second part of this study (Dong et al., 2023).

4.2 Processing of foods

Besides the contents of the nutrients, the processes to which they are exposed and their packaging are also effective in changing the numbers of AGEs they contain. It is known that the number of AGEs in foods increases because of heat treatments, especially at high temperatures. The reason for this condition can be explained as an increase in the speed of the Maillard reaction, which is a stage of glycation, because of an increase in temperature. Based on this information, it can be said that the amount of AGEs in foods such as sweets, fast food, and baked goods processed at high temperatures is higher than normal. Another factor that affects the Maillard reaction is high humidity. As the humidity level increases, a decrease in the reaction rate is observed because the dilution of the reactants in the water phase is achieved. As a result, while cooking with dry heat promotes the formation of AGEs, they can be reduced by baking in an oven at high humidity. For example, an egg cooked at medium heat and in a short time contains half the AGEs compared with eggs cooked by the same method but at a high temperature. Therefore, reducing the formation of AGEs, especially during cooking, grilling, and frying, methods such as deep frying and roasting should be avoided. Instead of these methods, methods such as boiling and lean cooking should be returned. In addition to these methods, shorter cooking times and lower cooking temperatures also reduce the formation of AGEs (Sharma et al., 2015; Burak et al., 2022).

In addition, substances such as spices are also known to be effective in the formation of AGEs in foods. According to previous studies, adding fructose or lactose to meat during sterilization significantly increases CML and CEL levels in heated meat samples. These results show that sugars can react with free amino acids, which facilitates the formation of AGEs. In another study, fat, nitrite, and erythorbate were added to minced beef meat, and the formation of CML and CEL in minced meat was examined. As a result, it has been observed that the formation of CML and CEL during cooking increases with the addition of fat and erythorbate but is inhibited by nitrite. This is because the result of fats in foods is an increase in oxidation, and in this case, it increases the formation of AGEs. The addition of salt and fat to food increases oxidation. Nitrite, on the other hand, inhibits oxidation because of its antioxidant property, which can prevent the formation of AGEs (Huang et al., 2023).

Conversely, it is inevitable that pasteurization and sterilization processes performed in dairy products affect the formation of AGE. Pasteurization is a thermal sterilization method used to kill harmful microorganisms in dairy products. A study has shown that the amount of furosine found in dairy products increases because of pasteurization, which further indicates that the heat process promotes the production of AGEs. Thermal processes in dairy products, such as heating and microwave processing, also increase the formation of AGEs. Non-thermal processing methods developed recently to prevent the formation of AGEs [pulsed electric field (PEF), carbon dioxide technology, ultraviolet light, etc.] exist, but the reliability of these technologies is insufficient. There is another system that inhibits the production of AGEs in the processing of dairy products, and this is pressure. In a previous study, it was observed that both pathogenic microorganisms and AGEs decreased because of high hydrostatic pressure (MHHP) processes with pre-incubation at moderate temperature in milk (Wu et al., 2023; Dong et al., 2023).

Yu and his colleagues (2023) noticed in a study that the amount of AGEs in pork meatballs that they kept in the freezer increased day by day (Yu et al., 2023). This indicates that myofibrillar protein oxidation increases with increasing frozen storage times of raw pork and that changes in protein structure occur. These results suggest that stored raw pork may increase CML and CEL levels in meaty balls and that these changes occur during frozen storage periods of raw pork. Huang and his friends examined the formation of CML in chicken and storage and observed that the amount of CML increased during storage in raw and boiled chicken. Considering these studies, an increase in AGE formation can be observed due to conditions such as protein and lipid oxidation, enzymatic reactions, and free amino acid formation in the storage process in general. Therefore, it is important for human health to act by following the rules required for storing food groups that tend to deteriorate quickly, such as meat and milk (Huang et al., 2022; Yu et al., 2023).

5. Conclusion

In this review, while focusing on the formation mechanisms of advanced glycation, the cellular damages it causes, and its impact on diseases, we also investigated how nutrition and food processing technologies affect the occurrence of this reaction. In particular, we delved into the detailed examination of AGEs and their influence on the formation of various cancer types, an aspect with limited prior research. The findings obtained supported the potential harmful effects of AGEs on human and societal health. Simultaneously, these findings provide evidence that nutrition and food technologies contribute to exacerbating this risk. In conclusion, starting with its broad outlines, we thoroughly evaluated AGEs and their products, aiming to elucidate the reasons for the formation and consequences of these reactions for the reader.

6. Conflict of Interest

The authors do not declare any conflicts of interest.

7.References

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